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Ultra-High-Frequency Left Prefrontal Transcranial Magnetic Stimulation as Augmentation in Severely Ill Patients with Depression: A Naturalistic Sham-Controlled, Double-Blind, Randomized Trial

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Key Words
Repetitive transcranial magnetic stimulation · Ultra-high-frequency stimulation · Major depression · Cognitive function

Abstract
Background and Aim: Repetitive transcranial magnetic stimulation (rTMS) is supposed to be not as effective in severe depression as it is in medium depression. We evaluated the treatment response to an ultra-high-frequency (UHF; 30 Hz) approach, which was used to maximize the rTMS efficacy in severely ill patients. ***Methods:*** 43 severely depressed patients were included in the randomized, double-blind study and received either rTMS with 30 Hz over the left dorsolateral prefrontal cortex or sham condition for 3 weeks as an add-on therapy to stable antidepressant medication. Hamilton Depression Rating Scale (HDRS) and cognitive performance were evaluated before and after the intervention. ***Results:*** In the active UHF group, the HRDS score was reduced by about 7.2, whereas the sham condition showed a smaller reduction of the HDRS score with 3.9. However, lithium as a covariant was responsible for the outcome difference, not the group of stimulation. No adverse events were reported. Comparing the differences of both groups in the pre- and post-study performance in a trail-making test, a group effect for the UHF group that was not influenced by the lithium intake was observed. ***Conclusion:*** A 30-Hz left prefrontal rTMS in severely depressed patients was safe and no adverse events occurred. Due to a strong effect of lithium as a covariate, we could not demonstrate favorable antidepressant effects of the UHF stimulation compared to sham. However, we found an improvement of processing speed performance in the UHF group, which covaried with improvement of psychomotor retardation.

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) has transformed from a neurological research tool into a highly promising treatment alternative in psychiatry. Especially in the therapy of major depressive disorder, the noninvasive rTMS has reached considerable attention with milestones like the first clinical trial [1], the approval by the US Food and Drug Administration [2] or the publication of the to date largest multisite study [3] within the last two decades. Alternatives to antidepressants are urgently needed, as about one third of patients will not remit with their first antidepressant challenge and 15% of the patients with depression are not helped at all by antidepressant medication. Existing data regarding antidepressant efficacy of rTMS are somewhat inclusive, meaning that there are many reports that were able to demonstrate antidepressant effects [3–7], but equally reports that could not show superiority to sham treatment or arguable clinically relevant effects [8–12]. However, the majority of meta-analyses concludes that rTMS is superior to sham in the treatment of depression [13–17]. Most studies agree that the differential influence of intensity, duration, and frequency of rTMS on antidepressive efficacy has not been fully explored so far. rTMS is supposed to be more successful in patients whose degree of depression is rather mild to medium than severe. Unfortunately, in severely depressed patients, treatment resistance is frequent and new options are most valuable especially for this population.

We evaluated the treatment response to an ultra-high-frequency (UHF; 30 Hz) approach over the left dorsolateral prefrontal cortex, which was used to maximize the rTMS efficacy in severely ill patients. A 30-Hz stimulation frequency is about 50% higher than the usual high-frequency stimulation, but considering the large number of subjects and patients who have undergone rTMS studies and the small number of seizures, the risk of rTMS to induce seizures is certainly very low [18, 19]. Fifty hertz was already used in patients with Parkinson's disease; 30 Hz is to our knowledge the highest frequency used to analyze antidepressant characteristics in patients with depression. An animal study with a model of depression that compared 20- and 30-Hz stimulation already suggested that the effectiveness of rTMS may be augmented by increasing the frequency of rTMS impulses [20].

In order to create 'real world' conditions, we used a naturalistic augmentation or add-on study, with patients continuing the antidepressant medication they already took before the study, but that had not led to a response.

Methods

Patients

The present study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and written informed consent was obtained from all participants before inclusion in the study. There were two cohorts (n = 26 and n = 17) with a total sample of 43 depressed subjects (16 males and 27 females), who were recruited between 2007 and 2009 from the Department of Biological Psychiatry and Neuroscience, Evangelical Clinics Gelsenkirchen, Germany. Inclusion criteria were beneath the present primary diagnosis of at least a moderate depressive episode with a minimum of 20 points on the HDRS without psychotic features (DSM-IV: 296.52, 296.53, 296.32, 296.33, 296.22, or 296.23), age from 18 to 75 years and both a certain stability of the course (no relevant change in the week before the start of the study) and stability of antidepressant medication (intake of either venlafaxine or mirtazapine over at least 3 weeks). Exclusion criteria were a history of seizures, moderate to severe head traumas or brain surgery, current other psychiatric disorders, current severe neurological or medical diseases or the implementation of a pacemaker. Before inclusion, internal and neurological examinations and additionally laboratory and EEG were performed.

In order to facilitate a clinical realistic study, all patients received an antidepressant pharmacological standard treatment with either venlafaxine or mirtazapine and additional standard inpatient treatment as usual. Inclusion was possible after at least 3 weeks of stable intake of one of these antidepressants. The allowed concomitant medication was lithium, when already established at least 4 weeks before inclusion, lorazepam up to 1.5 mg/day and antipsychotics. Anticonvulsive mood stabilizers were not allowed throughout the study.

Baseline stability is an important issue regarding minimizing bias through placebo response and naturalistic course; in order to exclude patients who got better without intervention, it was necessary that the HDRS score did not improve over 20% between 1 week before stimulation and at the day of the first scheduled stimulation. If an improvement over 20% occurs and the inclusion criteria are still fulfilled, the study intervention is postponed another week. Then baseline stability is checked again, and if there is still an improvement over 20%, the patient is excluded from the study.

Outcome Measures

The primary endpoint of the study was a clinician-rated measure of depressive symptoms with the HDRS (21-item version). Weekly rating was performed by the psychiatrist on ward, who had daily contact with the patient, but was not involved in the study at all and was not aware of the patient's group (active stimulation or sham), thus resulting in a double-blind condition.

Secondary outcome parameters were the self-reported measure of depressive symptoms using Beck's Depression Inventory (BDI) and performance using three cognitive tests, namely the Zahlen-Verbindungs-Test (ZVT), a cognitive test that included a trail-making test challenging processing speed [21], the Syndrom-Kurztest (SKT), a brief neuropsychological test battery for the assessment of potential deficits in memory and attention [22], and the Mehrfachwahl-Wortschatz-Test Version B, a multiple-choice verbal intelligence test estimating the premorbid intelligence lev-

el. Another parameter was patient satisfaction with the rTMS treatment measured with a visual analogue scale after the completion of the study.

Evaluation of all outcome parameters took place before the rTMS treatment and after completion of 3 weeks of stimulation. Another outcome parameter was if the patient could be considered as 'responder', which is defined as a reduction of at least 50% in HDRS score, or as 'remitter', which is defined as an HDRS score <8.

rTMS Treatment

rTMS was administered using a MagPro stimulator (Dantec, Denmark) with a figure-of-eight coil with an outer diameter of 97 mm. Prior to the initial rTMS session, the resting motor threshold was determined as the lowest intensity that could induce an involuntary movement of the abductor pollicis brevis muscle in at least 3 out of 6 times. Stimulation was applied at 110% of the motor threshold. Coil positioning was determined by the 10–20 EEG system, such that F3 corresponds to the left dorsolateral prefrontal cortex [23]. We chose two different, alternated randomized stimulus conditions. Stimulation was performed for 3 weeks on each workday (total of 15 sessions).

Left-side UHF (30 Hz) stimulation was applied in 20 trains of 3-second duration with 57-second intertrain intervals, resulting in 1,800 pulses per session. This condition was regarded as the active treatment with hypothesized antidepressant efficacy.

Left-side low-frequency (LF; 1 Hz) stimulation was applied in 11 trains of 90-second duration with 30-second intertrain intervals, totalling 990 pulses per session. That condition was regarded as the not active, sham treatment.

Statistical Analysis

All statistics were performed using STATA® (version 11; StataCorp, Tex., USA) at a significance level of 0.05, except for the three cognitive tests, where we corrected for multiple testing with Bonferroni correction with a significance level of 0.05/3 = 0.017. Baseline differences between the two groups were analyzed with the two-tailed paired t tests or, if appropriate, with Pearson's χ^2 test. Comparisons of the outcome parameters (HDRS, BDI, ZVT, SKT, Mehrfachwahl-Wortschatz-Test Version B) before and after the rTMS treatment were analyzed with two-tailed paired t tests. Comparisons between the two stimulation groups were carried out with one-way ANOVA, including possible covariates.

Results

Characteristics of the Study Population

We could include altogether 43 subjects in two cohorts. Unfortunately, the second cohort (n = 17) lacks information about the intake of lithium, benzodiazepines and antipsychotics during the study. There were no significant baseline differences in the two cohorts. Twenty-two subjects were randomized for the UHF group and 21 subjects for the LF group. No patient was excluded due to insufficient baseline stability. Demographic and baseline clinical information are shown in table 1.

Table 1. Demographic data of both groups

	UHF (active)	LF (sham)	p
Number	22	21	
Male/female, %	31.8/68.2	42.9/57.1	0.45
Age, years	56.9 ± 10.2	54.1 ± 7.8	0.31
HDRS score before rTMS	30.4 ± 4.8	28.2 ± 3.9	0.12
BDI score before rTMS	32.0 ± 11.9	29.0 ± 9.6	0.37
Stimulus intensity, %	43.4 ± 2.9	43.2 ± 2.0	0.87
Duration of illness, years	6.9 ± 3.4	6.4 ± 6.0	0.75
Lithium, %	31.3 (n = 16)	0.0 (n = 10)	0.05
Antipsychotics, %	81.25 (n = 16)	50.0 (n = 10)	0.09
Benzodiazepines, %	87.50 (n = 16)	50.0 (n = 10)	0.04

Data are presented as means with standard deviation.

In the UHF group, 68.2% were female and the average age was 56.9 years (SD: 10.2). The baseline HDRS score was 30.4 (SD: 4.8) and the baseline self-rated BDI score was 32.0 (SD: 11.9). In the LF group, 57.1% were female and the mean age was 54.1 (SD: 7.8). The HDRS mean score before the treatment was 28.2 (3.9) and the BDI mean score was 29.0 (SD: 9.6). The stimulus intensity and the duration of illness did not differ in the two groups [stimulus intensity: UHF, 43.4% (SD: 2.9) and LF, 43.2% (SD: 2.0); duration of illness: UHF, 6.9 years (SD: 3.4) and LF, 6.4 years (SD: 6.0)]. However, 33.8% of the patients in the active UHF group were taking lithium during the study, but no patient in the sham LF group did (p = 0.049) and benzodiazepine intake was significantly more often observed in the active group [UHF: 87.5% and LF: 50.0% (p = 0.04)]. Antipsychotics were taken during the study by 81.3% of patients in the UHF group and by 50.0% of the subjects in the LF group (p = 0.09).

Safety

Thirty-hertz UHF was well tolerated by the participants. All patients completed the study and no seizure occurred. No adverse events were reported by the patients. In the patient satisfaction of the treatment measured with a visual analogue scale, we found no difference between the two groups [F(1, 41) = 0.03, p = 0.86; data not shown].

Clinical Outcome Parameters

The clinical outcome parameters are presented in table 2. The primary endpoint of the study was the difference between the baseline HDRS score and the final

Table 2. Clinical outcome data of both groups

	UHF (active)	LF (sham)	p
Final HDRS score	23.1 ± 5.7	24.3 ± 5.7	0.48
HDRS score difference	7.2 ± 4.2	3.9 ± 3.8	0.01[a]
Without lithium	5.7 ± 2.3	3.9 ± 3.8	0.11
HDRS score reduction, %	23.9	13.8	–
Without lithium	18.8	13.8	–
Final BDI score	32.0 ± 11.9	29.0 ± 9.7	0.60
BDI score difference	6.3 ± 6.3	5.3 ± 7.1	0.62
Remission	0	0	–
Response	4[a] (18.2%)	0	0.32

Data are presented as means with standard deviation.

[a] 3 out of 4 patients with response in the active treatment group were taking lithium during the study.

Table 3. Outcome of the cognitive tests in both groups

	UHF (active)	LF (sham)	p
ZVT			
Baseline	166 ± 64.5	139.1 ± 47.8	n.s.
Final	145.4 ± 60.4	131.7 ± 48.8	n.s.
Difference	20.6 ± 16.7	2.1 ± 27.4	0.010
SKT			
Baseline	7.6 ± 5.7	4.9 ± 3.3	–
Final	4.9 ± 5.5	3.8 ± 3.8	–
Difference	2.5 ± 2.3	1.3 ± 1.6	0.064
Mehrfachwahl-Wortschatz-Test Version B			
Baseline	31.4 ± 2.1	34.6 ± 2.1	–
Final	35.3 ± 2.6	37.4 ± 2.7	–
Difference	3.9 ± 3.8	2.8 ± 4.7	0.385

Data are presented as means with standard deviation. n.s. = Not significant.

HDRS score after the study. The final HDRS score after 3 weeks of add-on rTMS was 23.1 (SD: 5.7; range: 12–34) in the active group and 24.3 (SD: 5.7; range: 11–35) in the sham group. Both groups showed an improvement of symptoms measured by the HDRS; the active, UHF group showed an average reduction of the HDRS score of 7.2 (SD: 4.2; range: 2–17, $p < 0.001$), whereas the sham condition, LF group showed a significantly smaller reduction of the HDRS score of 3.9 (SD: 3.8; range: 0–13, $p < 0.001$) [$F(1, 41) = 7.5$, $p = 0.009$]. However, lithium as a covariant, which was unequally distributed between the two groups despite randomization, was responsible for the difference in outcome [$F(1, 23) = 13.8$, $p = 0.001$], but not the group of stimulation [$F(1, 23) = 0.3$, $p = 0.58$]. Other covariates such as sex, age, antipsychotic or benzodiazepine intake had no significant influence on the results.

Due to the strong lithium influence, the HDRS score between the patients who took lithium [n = 5; HDRS score difference: 12.6 (4.7)] and those who did not [n = 11; HDRS score difference: 6 (2.3)] within the UHF group was compared and a statistically significant difference was found [$F(1, 15) = 14.85$, $p = 0.0018$].

In a subgroup analysis, patients were divided into two groups: very severely depressed with an HDRS score ≥30 [n = 21, HDRS score: 33.0 (SD: 2.5)] and severely depressed patients with an HDRS score <30 [n = 22, HDSR score: 25.9 (SD: 2.8)]. In both subgroups, we found no superiority of UHF compared to LF stimulation [severely depressed patients: $F(1, 20) = 2.55$, $p = 0.13$ and very severely depressed patients: $F(1, 10) = 0.2$, $p = 0.66$)], when considering the lithium covariate.

The difference between baseline and final BDI score showed an amelioration of self-perceived depressive symptoms over the study in both groups [UHF: 6.3 (SD: 6.3), $p < 0.001$; LF: 5.3 (SD: 7.1), $p = 0.003$]. However, there were no differences between the active and the sham group [$F(1, 41) = 0.26$, $p = 0.62$]. There were no patients in both groups who reached the state of remission after the study. Four patients reached the criteria defined as response; all were in the UHF group, and 3 of them were taking lithium.

Cognitive Parameters

The cognitive parameters are summarized in table 3. While the sham (LF) group showed no difference in the pre- and post-study performance in the ZVT (2.1; SD: 27.4, $p = 0.21$), the active group showed a significant improvement of the cognitive performance in this test (20.6; SD: 16.7, $p < 0.0001$). Comparing the differences of both groups, we found a clear-cut group effect for the UHF group [$F(1, 41) = 7.2$, $p = 0.010$] that was not influenced in a significant manner by the lithium intake and was significant even after correction for multiple testing.

In the SKT, we found an improvement of test performance in the post-study test compared to the baseline test before the stimulation in both groups [UHF: 2.5, SD: 2.3, $p < 0.001$; LF: 1.3 (SD: 1.6), $p = 0.008$], but no significant group difference [$F(1, 41) = 3.6$, $p = 0.06$].

Similar to the SKT, in the Mehrfachwahl-Wortschatz-Test Version B, we found an improvement over time in both groups [UHF: 3.9 (SD: 3.8), $p < 0.001$; LF: 2.8 (SD:

4.7), p = 0.015], but no group difference [F (1, 41) = 0.77, p = 0.39].

As we could show a stable group difference in the ZVT, a trail-making test, but not in the other cognitive tests, we assumed that the unique component of the ZVT is processing speed. We hypothesized, that rTMS might lead to an amelioration of psychomotor retardation measured by the change of item 8 in the HDRS. Thus we found a significant influence of the covariate 'psychomotor retardation' on the performance in the ZVT [F (2, 24) = 4.54, p = 0.044]. However, the effect was not strong enough to produce a group difference of the improvement of psychomotor retardation measured by the change of item 8 of the HDRS [F (1, 31) = 0.04, p = 0.84].

Discussion

In this randomized, double-blind trial, the patients received 3 weeks of rTMS treatment additionally to a concurrent stable antidepressant medication that alone did not lead to a significant antidepressant response. UHF stimulation at the left dorsolateral prefrontal cortex was considered as the active treatment, whereas left LF stimulation was considered as the nonactive, sham treatment.

In this rTMS study, we present two innovations: we recruited a sample of the most severely depressed patients with a baseline HDRS score (21-item version) of about 30 in the active treatment group. In the literature, an HDRS score of at least 25 is already considered as severely depressed [24, 25]. To our knowledge, no published randomized rTMS study with depressed patients had a higher HDRS baseline score. Because there are doubts about the potency of rTMS in such a severely depressed sample [26, 27], we wanted to provide maximum power of the rTMS method by raising the stimulus frequency up to 30 Hz, which we consider as UHF. In an animal model of depression, the forced swim test, different frequencies were tested for their antidepressant effects. All tested frequencies (1–25 Hz) showed antidepressant efficacy comparable with the potency of imipramine. The findings suggest that the antidepressant effect of the higher frequencies is likely to be sustained [28]. To our knowledge, in the already published, randomized studies, frequencies up to 20 Hz were used, thus our approach is 50% higher than the already quite established paradigms. Safety data already exist for the 50-Hz stimulation approach from a study with patients suffering from Parkinson's disease [29].

In both groups, the patients showed an improvement over the 3 weeks of the study phase, but the difference between UHF and LF was based on the lithium effect or on the combination of lithium and rTMS, but not on a superior stimulation frequency. Unfortunately, there were 31.3% of patients in the UHF groups who were taking lithium, and no patient in the LF group. Especially the lithium patients showed a good response that resulted in a detectable group effect. Improvement in terms of HDRS score reduction in both groups was in the range of previous studies; however, only 18.2% in the UHF group showed a response to treatment – and only 4.6% without lithium intake. This is considerably less than compared to other studies with not so severely depressed patients [3, 30].

In spite of randomization, unequal distribution of important variants is a not uncommon problem in small sample studies. However, there are several other reasons why identification of a group difference failed. We designed this study as an add-on study in order to provide more naturalistic data, but in add-on trials, it is known that the sham response is higher than in studies without concomitant antidepressant medication and sham response is known to be considerably large [31]. In fact, with a similar add-on design, a multicenter study with 127 patients investigating antidepressant efficacy failed to demonstrate beneficial results [32]. However, other add-on studies with patients who were also severely depressed could demonstrate superiority of active treatment over sham treatment, with 5 and 10 Hz, respectively [6, 33, 34].

Secondly, the sham group showed HDRS and BDI score improvement over the study time, which could be a placebo response or the natural course of patients, whose depressive symptoms were severe but who were not considered treatment-resistant as per definition [35]. The sham group got left LF stimulation, thus making it very difficult for the participants to figure out, which treatment they received. That is why we can assume that participants showed full placebo response of this kind of suggestive method, which might make it even more difficult to detect possible existing group differences. Some authors share the opinion that nonpharmacological interventions might produce a greater placebo response than pharmacological ones [36], but others state that placebo rates decrease with severity of depression [37, 38]. Furthermore, it cannot be ruled out that our sham condition also demonstrated some antidepressant effect, as LF rTMS also has an effect in the regional cerebral flow [39]. However, choosing a sham condition is a trade-off between effective blinding and truly inactive 'stimulation'

[40]. At least from a clinical point of view, our sham approach did not reveal any relevant effects. No patient from the sham group worsened and the response in the sham group with a mean score reduction of 3.9 in the HRDS was within the reported limits of other groups [3, 33].

Another possible explanation for the negative finding is that the study duration of 3 weeks was simply not long enough to develop a group difference without the lithium covariant. Longer treatment duration seems to be better in terms of antidepressant efficacy [41, 42] and two other studies with very severely depressed patients who had a baseline HDRS score of about 30 and a positive finding treated the patients between 4 and 6 weeks [2, 33]. That is supported by our finding that the cognitive performance in one test (ZVT, trail-making test character) improved considerably in the active treatment group independent from an antidepressant effect of rTMS, while it did not in the sham group. In this test, processing speed was involved, which is known to be considerably disturbed in major depression [43], but was no major compound in the two other psychological tests, in which no group difference occurred. Improved performance in trial-making tests could point towards an amelioration of frontal lobe deficits, which might be an effect of the UHF stimulation. rTMS has already shown to improve cognitive function in Alzheimer's disease [44]. Additionally, rTMS might specifically target psychomotor retardation as a core symptom of depression, thus resulting in fast and better performance in speed processing tasks, which are valid measurements for psychomotor retardation [45, 46]. Two studies already reported that despite a lack of efficacy in terms of HDRS score reduction, high-frequency rTMS (10 and 20 Hz, respectively) significantly decreased scores on the psychomotor retardation scales [10, 47], whereas another study did not find such associations. In our study, we found a significant influence of the covariate 'psychomotor retardation' (quantified by HRDS item 8) on the performance in the trail-making test, thus pointing towards the fact that reduction in psychomotor retardation might be an early step of antidepressant response, similar to some antidepressants.

Another finding worth mentioning is that in the active UHF group, the patients who took lithium had a higher HDRS score reduction than those patients who did not take lithium. This was not necessarily expected, because patients taking lithium were only included in the study, if lithium had already been given for at least 4 weeks before the start of the stimulation. Although very preliminary, our finding might suggest that lithium is a favorable concomitant medication in rTMS and that the combination might facilitate more effects than lithium or rTMS alone.

Limitations of the study are the unequal distribution of lithium intake, which in combination with the modest sample size unfortunately limits the informative value. Another problem of the study is the additional intake of benzodiazepines and antipsychotics, which was either unequally distributed or the information about the intake was missing. In studies investigating antidepressant effects, the use of these two groups of drugs is problematic, because both are known to be able to improve sleep and anxiety, without having clear-cut antidepressant effects, perhaps with quetiapine as an exception. Therefore, antipsychotics might reduce the HDRS score with its three sleep-related items, without unique antidepressant effects.

In summary, 30-Hz left prefrontal rTMS in severely depressed patients was safe and no adverse events occurred. Due to unequal distribution of lithium, we were not able to demonstrate an antidepressant group difference compared to sham. However, we found an improvement of processing speed performance in the stimulation group, which covaried with the improvement of psychomotor retardation. Treating severely depressed patients with rTMS could not be discarded based on our data, especially when bearing in mind that even a mild or modest amelioration, which rTMS could deliver in combination with antidepressants, might have a relevant clinical effect in terms of suicidal prevention or regaining the ability for psychotherapeutic work.

Future clinical research in rTMS for affective disorders has to deal with many aspects. Studying the impact of stimulation parameters (e.g. frequency or intensity) on the efficacy in order to optimize rTMS treatment [48] is definitively one of them, and exploring favorable concomitant medication is another one. Alternative approaches that have been developed in the last few years, and might contain even more potential than the 'conventional' rTMS method, are important and promising research issues, too. Theta burst stimulation is one of them and involves the repetitive application of very short trains at high frequency (50 Hz) and very short intertrain intervals [49], which is therefore still different from our approach. Preliminary data suggest that theta burst stimulation is a safe method [50] and may have antidepressant effects [51, 52].

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